REMARKS

Preliminary Remarks

Claims 17-19, 21, 22 and 58-62 are pending. Claim 22 is withdrawn. Applicants appreciate the courtesy extended by the Examiner in withdrawing the requirements to elect a specific megalin-binding moiety, therapeutic agent and neurodegenerative disease.

Support for the amendments to the claims to recite megalin-binding RAP fragments is found throughout the specification, including at page 8, lines 1-6 (indicating that megalin ligands include RAP polypeptide at least 80% identical to the native protein over a length of at least 100 amino acids), page 39, line 12 (referencing amino acids 221-323), page 42, lines 27-32 (referring to natural or modified megalin binding ligands), page 35, lines 26-27 ("LRP" refers generally to members of the LRP family) and page 40, lines 24-28 ("RAP fragment as used herein includes, but not limited to, any portion of RAP or its biologically equivalent analogs that contains a sufficient portion of the ligand to enable it to bind to LRP and to be transcytosed, transported across the blood-brain barrier"). The 323 amino acid sequence of mature RAP is set forth in Figure 15.

The Examiner's rejection of the claims under 35 U.S.C. 112, second paragraph, is mooted by amendment of claim 18 to add an administration step.

The rejection under 35 U.S.C. 112, first paragraph: enablement

The Examiner rejected the claims as assertedly lacking enablement for the claimed breadth of all megalin binding moieties. The Examiner asserted that the only working examples were of RAP-conjugated enzymes and that it would require undue experimentation to make the starting materials required for the claimed method. Solely in order to expedite prosecution, Applicants have amended the claims to recite a megalin-binding RAP fragment comprising an amino acid sequence least 80% identical over its length to a domain 3 fragment of RAP.

Applicants respectfully submit that the application provides ample guidance to enable one of ordinary skill in the art to truncate RAP and prepare modified RAP fragments, to conjugate such polypeptides to therapeutic agents, and to administer such agents, without undue experimentation. See, for example, the guidance at pages 37-40, pages 42-45, pages 61-69, page 72, and pages 80-82, as well as the working embodiments illustrated in the Examples.

The application specifically contemplates a number of different RAP fragments (see page 39, lines 10-25; see also SEQ ID NO: 2, which is a 28 kDa C-terminal fragment of RAP). The application also teaches that fragments including analogs of RAP are readily produced (see, e.g., references cited at pages 38-39). The application contains an alignment (Figure 14) showing conserved residues among human, mammalian and other species (see page 38, lines 1-11). The application teaches at page 37-40 and pages 80-82 the generation of fragments including analogs as well as the generation and screening of libraries of modified megalin ligands such as RAP (see page 72, lines 12-25). Finally, the application teaches at pages 42-45 and 61-69 the conjugation (including fusion) of megalin ligands such as RAP fragments to active agents.

Provided herewith is evidence in the form of a Declaration Under 37 C.F.R. 1.132 of Todd Zankel (Exhibit A) that production of a RAP fragment consisting of amino acids 201-319 of SEQ ID NO: 1 was readily accomplished with only routine effort. This fragment bound to megalin with an affinity equivalent to full length mature RAP.

Applicants respectfully submit that in view of the knowledge and relatively high level of skill in the art (which already permitted production of truncated RAP and analogs), and in view of the guidance in the specification as well as the multiple working examples, it would have required only routine effort for one of ordinary skill in the art to make and use the claimed invention. Thus, the rejection of the claims for asserted lack of enablement should properly be

withdrawn.

The rejection under 35 U.S.C. 112, first paragraph: written description

The Examiner rejected the claims as assertedly lacking written description for the claimed breadth of all megalin binding moieties lacking defined structure. As noted above, solely in order to expedite prosecution, Applicants have amended the claims to reference a sequence, thus providing a structural element, as well as functional properties (megalin-binding and improving transcytosis, or improving transport to the brain).

The application describes a representative number of species falling within the claimed genus. The application specifically contemplates a number of different RAP fragments (see page 39, lines 10-25; see also SEQ ID NO: 2, which is a 28 kDa C-terminal fragment of RAP).

Thus, Applicants respectfully submit that the specification provides written descriptive support for the claims and the rejection may properly be withdrawn.

The rejection under 35 U.S.C. 102

The rejection of all claims under 35 U.S.C. 102(e) over Beliveau et al., U.S. Patent Application Publication No. 2003/0129186 and under 35 U.S.C. 102(a) over Beliveau et al., Int'l Publication No. WO 03/009815 may properly be withdrawn because neither of these cited references discloses all elements of the claims. Neither reference teaches or suggests that megalin is a receptor responsible for blood brain transport. In fact, the Beliveau et al. references suggest that megalin is not a receptor of interest (see paragraphs 312 and 324 of US 2003/0129186). Moreover, neither reference teaches that domain 3 fragments of RAP are desirable delivery vehicles for blood brain transport or that one should administer agents conjugated to megalin-binding RAP fragments as claimed.

The rejection of claim 18 under 35 U.S.C. 102(b) over Czekay et al. is mooted inasmuch as the rejection was based on the absence of an administration step in the claim, and the claim now recites an administration step.

The rejection of claims 17-19 under 35 U.S.C. 102(b) over Zlokovic as evidenced by Schenck is mooted by the amendment of the claims. The Examiner characterizes Zlokovic as teaching complexes comprising apo J (a megalin ligand) and beta-amyloid(1-40), and cites Schenck for its discussion of beta-amyloid. Such Apo J complexes are not relevant to the present claims, which reference RAP.

For these reasons, the rejections of the claims as assertedly anticipated by the cited art should properly be withdrawn.

The rejection under 35 U.S.C. 103

The rejection of all claims under 35 U.S.C. 103 over Beliveau, U.S. Patent Application Publication No. 2003/0129186, or alternatively over Beliveau, Int'l Publication No. WO 03/009815, in combination with Perez-Navarro, may properly be withdrawn because none of the references, even in combination, disclose or suggest all elements of the claims.

The Examiner cites Perez-Navarro as teaching use of BDNF for Huntington's disease. The cited Beliveau references and the Perez-Navarro reference all fail to disclose (1) that megalin is a receptor responsible for blood brain transport, (2) that domain 3 fragments of RAP are desirable delivery vehicles for blood brain transport, and (3) administration of agents conjugated to megalin-binding RAP fragments as claimed. Thus, no *prima facie* case of obviousness can be established because the cited art fails to suggest all elements of the claims.

The various rejections of all claims under 35 U.S.C. 103 over Zlokovic in combination with other references is not relevant for the reason discussed above, i.e. apo J is not

relevant to the present claims. Neither Zlokovic nor any of the references combined with Zlokovic disclose or suggest administering agents conjugated to fragments of RAP as claimed. Zlokovic expresses uncertainty regarding the identity of the receptor responsible for transport of apoJ. See p. 4233, second col., which suggests that the receptor may be different from the gp330/megalin found in other organs or even an entirely unrecognized receptor. Zlokovic also suggests at p. 4234, first col., that gp330/megalin on brain endothelial cells "might interact mainly or exclusively with apoJ." Thus, no *prima facie* case of obviousness can be established because the cited art fails to suggest all elements of the claims and also fails to provide a reasonable expectation of success for the claimed invention.

For all of these reasons, the rejections for asserted obviousness over the cited art should properly be withdrawn.

Conclusion

Applicants submit that the application is in condition for allowance and respectfully request notification of the same.

No fees are believed necessary in connection with this paper, but if any fees are necessary, the Commissioner is authorized to charge Marshall, Gerstein & Borun LLP deposit account number **13-2855.**

Respectfully submitted,

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